Nivolumab Combined with Ibrutinib for Relapsed, Refractory or High-risk Untreated Patients with Chronic Lymphocytic Leukemia (CLL)

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1.0 OBJECTIVES

Primary Objectives

1. To determine the efficacy (response rate) of nivolumab in combination with ibrutinib in patients with relapsed/refractory or high-risk untreated CLL by
   a. Cohort 1: determine the response rate (CR/CRi) by 2008 IWCLL criteria
   b. Cohort 2: determine the conversion rate from PR to CR/CRi by 2008 IWCLL criteria
   c. Cohort 3: determine the response rate (CR/CRi)

Secondary Objectives

1. To determine the safety of nivolumab in combination with ibrutinib in patients with relapsed, refractory or high-risk untreated CLL/Richter transformation (RT).
2. To determine the progression-free survival of patients with relapsed, refractory or high-risk untreated CLL/RT treated with nivolumab in combination with ibrutinib.
3. To determine the overall survival of patients with relapsed, refractory or high-risk untreated CLL/RT treated with nivolumab in combination with ibrutinib.

Exploratory Objectives

1. To study immunological and molecular changes in peripheral blood, lymph node, and bone marrow in response to nivolumab and ibrutinib therapy.

2.0 BACKGROUND

2.1 Chronic lymphocytic leukemia (CLL): CLL is the most common leukemia in the United States and Western hemisphere.[1] It is a disease of the aging population; the median age at diagnosis is 72 and over two-thirds of patients with CLL are over 60 years of age. Both the incidence and prevalence of this disease increase with age. The natural history for individuals with this disease is diverse. Generally, patients with early Rai stage (stage 0, low-risk) have a median expected survival of more than 10 years. Those with evidence of marrow failure manifested by anemia (stage III) or thrombocytopenia (stage IV) (Rai high-risk) have an estimated median survival of only 2 years. In patients with intermediate-risk disease (Rai stage I and II) the estimated median survival is 7 years. There is remarkable clinical diversity in patients with CLL. Following diagnosis, some patients have smoldering, asymptomatic disease that may not progress for many years; others are diagnosed with advanced stage, or early stage disease that rapidly progresses, causing symptoms and/or bone marrow failure and require treatment. Various genetic/molecular markers have been established and validated to help in prognostication and

are routinely used in clinical practice.[1] These include β2-microglobulin, cytogenetics, immunoglobulin variable heavy chain gene (*IGHV*) mutational status, zeta chain-associated protein 70 (ZAP-70) expression, and CD38 expression. Presence of deletion of the short arm of chromosome 17 [del(17p)] (and/or mutated *TP53)* is associated with the worst clinical outcomes in patients with CLL and considered high-risk disease features.[2-4] Patients with relapsed/refractory CLL constitute another group of patients with poor prognosis.[1,5] Richter transformation (RT) represents an aggressive transformation of CLL, and is associated with poor prognosis.[6,7] Treatment with chemoimmunotherapy, though commonly employed, is not very effective.[8] Recently, immunotherapy with PD-1 blockade was shown to be effective in patients with RT with 4 out of 5 patients responding to pembrolizumab.[9] These early results represent a major advance for patients with RT.

2.2 Immunotherapy in CLL: Immunotherapy has been an important part of CLL therapeutic armamentarium. Several strategies have been employed: a) use of monoclonal antibodies (mAb) such as anti-CD20 mAb (rituximab, ofatumumab, obinutuzumab) and anti-CD52 mAb (alemtuzumab)[10,11]; b) use of lenalidomide[12-14]; c) adoptive immunotherapy with an allogeneic stem cell transplant[15]; d) use of chimeric antigen receptor (CAR).[16] These studies highlight the fact CLL cells are amenable to immune-based therapies.

2.3 T cell dysfunction in CLL: Several studies have shown that CLL development and progression is associated with functional immune-defects in the T cell compartment.[11,13,14,17-21] Ramsay et al. showed that T cells isolated from patients with CLL have functional defects in F-actin polymerization leading to impaired formation of immunological synapses with antigen presenting cells (APCs).[13] Riches et al. reported that T cells from patients with CLL exhibit features of T cell exhaustion which results in progressive loss of T cell proliferative and cytotoxicity capacity.[14] Motta et al. reported increased expression of both surface and cytoplasmic cytotoxic T lymphocyte-associated antigen (CTLA-4, also known as CD152) in both CD4+ and CD8+ T cells from treatment naïve patients with CLL compared to normal donors.[18] Riches et al. recently reported increased expression of programmed death-1 (PD-1, also known as CD279) receptor in T cells of patients with CLL.[14] They also reported that PD-1 is preferentially expressed on $CD3^{+}CD8^{+}CCR7^{-}$ effector T cells. Unlike CTLA-4 whose predominant role is at the time of T cell activation, PD-1 predominantly regulates effector T cell function in the peripheral tissues.[22-24] PD-L1 (ligand for PD-1) is also over expressed in the CLL B cells.[17] The increased expression of CTLA-4 and PD-1 on T cells of patients with CLL and PD-L1 on the CLL cells contributes to impaired T cell function.

2.4 Anti-PD1 (Nivolumab, BMS-936558, MDX1106):

2.4.1 Mechanism of Action

Immune activation is tightly regulated by co-stimulatory (e.g. CD28 and ICOS) and co-inhibitory (e.g. CTLA-4 and PD-1) receptors expressed on T cells. Agonistic antibodies against co-stimulatory T cell receptors and blocking antibodies against co-inhibitory T cell surface receptors have both been shown to potentiate T cell activation for tumor cell killing.

PD-1 is mainly expressed by activated CD4+ and CD8+ T cells, as well as APCs. It has two ligands, PD-L1 and PD-L2, with distinct expression profiles.[25] PD-L1 is expressed not only on APCs, but also on non- hematopoietic cells, including tumor cells. Expression of PD-L2 is largely restricted to APCs including macrophages and myeloid dendritic cells, as well as mast cells. The role of PD-1 as a negative regulator of T cells was best demonstrated by the finding that PD-1 deficient mice developed significant autoimmunity with high titers of autoantibodies.[22,26] Subsequently, blocking antibodies against PD-1 were shown to activate immune responses that resulted in reduction of tumor metastasis and tumor growth in a number of experimental tumor models.[27,28] Consistent with the immune inhibitory role of PD-1/PD-L1/2 signaling, forced expression of PD-L1 in murine tumor cell lines allowed increased tumor growth in vivo, which was otherwise kept in check by T cells. The inciting effect of PD-L1 on tumor growth was reversed by blocking anti-PD-L1 antibodies.[29]

Nivolumab (BMS-936558) is a fully human, IgG4 (kappa) isotype, monoclonal antibody that binds PD-1. Blockade of the PD-1 pathway by nivolumab was studied using the mixed lymphocyte reaction (MLR). PD-1 blockade resulted in a reproducible enhancement of both proliferation and IFN-γ release in the MLR. The effect of nivolumab on antigen-specific recall response was investigated using a CMV-restimulation assay with human peripheral blood mononuclear cells (PBMCs), and was evaluated by ELISA. These data indicated that nivolumab, versus an isotype-matched control antibody, augmented IFN-γ secretion from CMV-specific memory T cells in a dose-dependent manner. PD-1 blockade by nivolumab is therefore considered a promising immunotherapeutic strategy.

2.4.2 Summary of Safety Results from Nivolumab Program

For a complete review of clinical information, please refer to the nivolumab Investigator Brochure.

2.4.2.1 Summary of Safety

The overall safety experience with nivolumab is based on experience in approximately 1500 patients as either a monotherapy or in combination with other therapeutics. In general for monotherapy, the safety profile is similar across tumor types. The one exception is pulmonary inflammation AEs which may be numerically greater in patients with NSCLC possibly because in some cases it can be difficult to distinguish between nivolumab-related and unrelated causes of pulmonary symptoms and radiographic changes. The most frequently reported treatment- related AE is fatigue which is almost always low grade.

The safety profile is generally consistent across completed and ongoing clinical trials with no MTD reached at any dose tested up to 10 mg/kg. There was no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. Most related AEs are thought to be due to the effects of inflammatory cells on specific tissues. Most AEs were low-grade (Grade 1 to Grade 2) with relatively few related high-grade (Grade 3 to Grade 4) AEs. Most high-grade events were manageable with use of corticosteroids or hormone replacement therapy (endocrinopathies).

2.4.2.2 Clinical Safety in Advanced Malignancies (Nivolumab Monotherapy)

A total of 306 patients with treatment-refractory malignancies were treated in a phase 1 multidose study (MDX1106-03, CA209003). This is an ongoing, phase I dose-escalation study of nivolumab monotherapy in patients with advanced solid tumors; 1, 3, or 10 mg/kg nivolumab and 0.1 and 0.3 mg/kg (included as part of Amendment 4) administered by IV Q2W; treatment up to 2 years. Results were published by Topalian et al. (NEJM 2012).[30] The baseline disease diagnosis by treatment for MDX1106-03 is provided in Table 2.4.2.2-1.

Table 2.4.2.2-1: Baseline Disease Diagnosis by Treatment - MDX1106-03

	No. of Patients					
Nivolumab (mg/kg)	**0.1 mg/kg**	**0.3 mg/kg**	**1 mg/kg**	**3 mg/kg**	**10 mg/kg**	**TOTAL**
Total N	**17**	**18**	**86**	**54**	**131**	**306**
NSCLC	0	0	33	37	58	128
Melanoma	17	18	35	17	20	107
RCC	0	0	18	0	16	34
mCRPC	0	0	0	0	17	17
CRC	0	0	0	0	19	19

Abbreviations: CRC: colorectal adenocarcinoma; mCRPC: metastatic castration-resistant prostate cancer; NSCLC: non-small cell lung cancer; RCC: renal cell carcinoma;

2.4.2.3 Adverse Events

There was no pattern in the incidence, severity, or causality of AEs related to the dose of nivolumab, between 1 and 10 mg/kg, in MDX1106-03. Of the 306 treated patients in MDX1106-03, 303 (99.0%) patients have at least 1 reported AE regardless of causality (Table 2.4.2.3-1). The most frequently reported AEs were fatigue (54.9%), decreased appetite (35.0%), diarrhea (34.3%), nausea (30.1%), and cough (29.4%). Treatment-related AEs were reported in 230 (75.2%) of the 306 patients. The most frequently reported treatment-related AEs were fatigue (28.1%), rash (14.7%), diarrhea (13.4%), and pruritus (10.5%). Most treatment-related AEs were low grade. **Treatment-related Grade 3-4 AEs were reported in 52 (17.0%) of patients.** The most frequently reported treatment-related high grade AE was fatigue (6.5%).

Table 2.4.2.3-1: Summary of Adverse Events Reported in ≥15% of All Treated Patients

	No. of Patients (%)			
Preferred Term	**AEs regardless of causality**		**Treatment-related AEs**	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Any AE	**303 (99)**	**127 (42)**	**230 (75)**	**52 (17)**
Fatigue	168 (55)	20 (7)	86 (28)	7 (2)
Decreased appetite	107 (35)	3 (1)	28 (9)	1(0.3)
Diarrhea	105 (34)	3 (1)	41 (13)	3 (1)
Nausea	92 (30)	9 (3)	27 (9)	2 (1)
Cough	90 (29)	4 (1)	11 (4)	1 (0.3)
Dyspnea	80 (26)	27 (9)	11 (4)	0
Constipation	78 (26)	2 (1)	5 (2)	0
Rash	74 (24)	0	45 (15)	0
Vomiting	70 (23)	7 (2)	10 (3)	1 (0.3)
Back pain	68 (22)	7 (2)	3 (1)	1 (0.3)
Arthralgia	63 (21)	4 (1)	15 (5)	0
Pyrexia	61 (20)	1 (0.3)	17 (6)	0
Headache	59 (19)	1 (0.3)	8 (3)	0
Edema peripheral	59 (19)	1 (0.3)	3 (1)	0
Dizziness	56 (18)	1 (0.3)	10 (3)	0
Pruritus	56 (18)	1 (0.3)	32 (11)	1 (0.3)
Weight decreased	48 (16)	1 (0.3)	11 (4)	0

2.4.2.4 Select Adverse Events

Select AE categories (events with a potential inflammatory mechanism requiring more frequent monitoring and/or unique intervention such as immunosuppressants and/or endocrine replacement therapy) include: GI AEs, pulmonary AEs, renal AEs, hepatic AEs, skin AEs, and endocrinopathies. In addition, Select AEs include a category for infusion reactions. These Select AEs are considered events of interest based on the mechanism of action and were previously referred to as immune-related AEs or immune-mediated AEs. The frequencies of these events are summarized in Table 2.4.2.4-1. The 10 mg/kg cohort had numerically greater frequency of high-grade select AEs including the subcategories of endocrinopathies, GI, pulmonary, and infusion reactions.

Table 2.4.2.4-1: Treatment-related Select Adverse Events by Treatment - All CTC Grades Reported in at Least 10 Treated Patients in MDX1106-03

Preferred Term	0.1 mg/kg n=17		0.3 mg/kg n=18		1 mg/kg n=86		3 mg/kg n=54		10 mg/kg n=131		Total N=306	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Any Select AE	**8 (47)**	**1 (5.9)**	**9 (50)**	**0**	**42 (49)**	**3 (4)**	**23 (43)**	**2 (4)**	**58 (44)**	**13 (10)**	**140 (46)**	**19 (6)**
Any Endocrinopathies	**4 (24)**	**0**	**2 (11)**	**0**	**9 (11)**	**0**	**4 (7)**	**0**	**10 (8)**	**3 (2)**	**29 (10)**	**3 (1)**
Endocrinopathies Thyroid	3 (18)	0	2 (11)	0	9 (11)	0	4 (7)	0	8 (6)	2 (2)	26 (9)	2 (1)
Blood TSH	2 (12)	0	1 (6)	0	2 (2)	0	2 (4)	0	4 (3)	1 (1)	11 (4)	1 (0.3)
Hypothyroidism	1 (6)	0	1 (6)	0	5 (6)	0	1 (2)	0	3 (2)	1 (1)	11 (4)	1 (0.3)
Any Skin AEs	**3 (18)**	**0**	**5 (28)**	**0**	**27 (31)**	**0**	**12 (22)**	**0**	**28 (21)**	**1 (1)**	**75 (25)**	**1 (0.3)**
Rash	3 (18)	0	3 (17)	0	20 (23)	0	5 (9)	0	14 (11)	0	45 (15)	0
Pruritus	0	0	1 (6)	0	15 (17)	0	3 (6)	0	13 (10)	1 (1)	32 (11)	1 (0.3)
Any GI AE	**1 (6)**	**0**	**2 (11)**	**0**	**19 (22)**	**0**	**7 (13)**	**0**	**14 (11)**	**3 (2)**	**43 (14)**	**3 (1)**
Diarrhea	1 (6)	0	2 (11)	0	19 (22)	0	6 (11)	0	13 (10)	3 (2)	41 (13)	3 (1)
Any hepatic AE	**0**	**0**	**2 (11)**	**0**	**8 (9)**	**0**	**3 (6)**	**2 (4)**	**5 (4)**	**2 (2)**	**18 (6)**	**4 (1)**
ALT increased	0	0	1 (6)	0	6 (7)	0	1 (2)	0	3 (2)	**1 (1)**	11 (4)	1 (0.3)
Any Pulmonary AE	1 (6)	**0**	1 (6)	**0**	**6 (7)**	**3 (4)**	**2 (4)**	**0**	**7 (5)**	**3 (2)**	**17 (6)**	**6 (2)**
Pneumonitis	1 (6)	0	0	0	4 (5)	2 (2)	1 (2)	0	6 (5)	2 (2)	12 (4)	4 (1)
Infusion reaction	**0**	**0**	**1 (6)**	**0**	**3 (4)**	**0**	**3 (6)**	**0**	**8 (6)**	**2 (2)**	**15 (5)**	**2 (1)**
Infusion-related	0	0	1 (6)	0	3 (4)	0	3 (6)	0	5 (4)	0	12 (4)	0
Hypersensitivity	0	0	0	0	0	0	1 (1.9)	0	3 (2)	2 (2)	4 (1)	2 (1)

2.4.2.5 Adverse Events Leading to Discontinuation

At least 1 treatment-related AE leading to discontinuation was reported in 32 (10.5%) of the 306 treated patients. Grade 3-4 treatment-related events were reported in 14 (4.6%) patients. The frequency of treatment-related AEs leading to discontinuation was not associated with the dose of nivolumab. Pneumonitis was the most common treatment-related AE leading to discontinuation (8 patients, 2.6%); pneumonitis reported in 3 (1.0%) patients was Grade 3-4. Treatment-related AEs reported in at least 2 patients included pneumonitis (8 patients, 2.6%), colitis (3 patients, 1.0%) and myalgia, hepatitis, hypersensitivity, and infusion-related reactions (each reported in 2 patients, 0.7%). One event of Grade 5 sepsis was reported for 1 subject, a 62-year-old male treated with 1 mg/kg nivolumab.

2.4.3 Summary of Efficacy (Nivolumab monotherapy)

The clinical activity data presented below are from MDX1106-03 (nivolumab monotherapy).
The data from melanoma cohort is shown below.[31]

Table 2.4.3-1: Responses Melanoma Patients - MDX1106-03

Dose (mg/kg)	N	ORR (%)	PFS (months)	OS (months)
0.1	17	35.3	3.6	16.2
0.3	18	27.8	1.9	12.5
1.0	35	31.4	9.1	25.3
3.0	17	41.2	9.7	20.3
10.0	20	20.0	3.7	11.7
All doses	107	30.8	3.7	16.8

2.4.3 Nivolumab monotherapy in Hodgkin's lymphoma

Ansell et al recently reported results of nivolumab monotherapy in patients with relapsed or refractory Hodgkin's lymphoma.[32] Twenty-three patients were treated (median age 35, range 20-54). A total of 22 patients had nodular sclerosis subtype of Hodgkin's lymphoma and one patient had mixed cellularity disease. About two-thirds of the patients had received 4 or more prior therapies. 78% had failed brentuximab vedotin and a similar number had failed prior autologous stem cell transplantation. Nivolumab was administered at 3 mg/kg IV every 2 weeks. Among the 23 patients, Grade 3 or 4 adverse events occurred in 12 patients (52%). Overall, drug-related adverse events were reported in 18 patients (78%). The most common were rash (in 22%) and a decreased platelet count (in 17%). Drug-related grade 3 adverse events, which were reported in 5 patients (22%), included the myelodysplastic syndrome, pancreatitis, pneumonitis, stomatitis, colitis, gastrointestinal inflammation, thrombocytopenia, an increased lipase level, a decreased lymphocyte level, and leukopenia. There were no drug-related grade 4 or 5 adverse events. Three patients had one serious drug-related adverse event each (grade 3 pancreatitis, grade 3 myelodysplastic syndrome, and grade 2 lymph-node pain). There were no treatment-related deaths. The rate of adverse events was similar to that in trials of nivolumab in patients with solid tumors.

The median number of nivolumab doses that patients received was 16 (range, 6 to 37), administered over a median treatment duration of 36 weeks. The response rate was 87%, with a CR occurring in 4 patients (17%), a PR in 16 patients (70%), and stable disease in 3 patients (13%). Of the 4 patients

with complete responses, 3 had not received previous treatment with brentuximab. The rate of PFS at 24 weeks was 86%. The median duration of follow-up was 40 weeks (range, 0 to 75).

2.5 Ibrutinib

2.5.1 B cell receptor (BCR) signaling plays a crucial role in the pathogenesis in CLL.[33-36] The BCR signaling pathway consists of immunoglobulin bound to the cell membrane that attaches to heterodimer consisting of CD79a and CD79b.[36-38] Binding of a ligand to the membrane immunoglobulin leads to recruitment and phosphorylation of spleen tyrosine kinase (SyK) and Src family kinase (Lyn), which in turn recruit and phosphorylate many kinases and adapter proteins including Bruton tyrosine kinase (BTK). BTK is a non-receptor tyrosine kinase of the Tec kinase family and plays a crucial role in BCR signaling.[39,40] BTK is expressed in non-T cell hematopoietic cell lineages.[41,42] The BTK gene is located on chromosome Xq21.33-q22 and mutations in this gene results in X-linked agammaglobulinemia, a condition characterized by marked reduction in mature B cells, severe hypogammaglobulinemia, and increased susceptibility to infections.[43] BTK activates downstream molecules such as nuclear-factor-kappa B and MEK/ERK, which are involved in many cellular processes including proliferation, survival, differentiation, apoptosis, and metabolism. Gene expression profiling has shown that BCR signaling is the most expressed signaling pathway in patients with CLL.[35] BCR signaling is enhanced in patients with poor prognostic markers such as ZAP-70 overexpression and those with unmutated immunoglobulin heavy chain gene (*IGHV*).[44,45]

2.5.2 Ibrutinib forms a specific bond with the cysteine-481 of BTK.[46] It leads to highly potent BTK inhibition with an IC50 of 0.5nM.[47] Treatment of CLL cells with ibrutinib induced apoptosis in a dose- and time- dependent manner which was independent of baseline cytogenetics, *IGHV* mutational status or baseline BTK protein expression.[48] Ibrutinib also induced apoptosis in normal B cells, but this was significantly less than that seen in CLL cells, indicating that CLL cells are more sensitive to ibrutinib than normal B cells. Ibrutinib treatment of CLL cells inhibited downstream signaling pathways including ERK1/2 phosphorylation, CD40L induced AKT phosphorylation and CD40L induced NF-kB DNA binding.[48] Ponader et al. evaluated the role of the tissue microenvironment of CLL cells and its effect on treatment with ibrutinib.[49] They reported that ibrutinib treatment significantly inhibited CLL cell migration and survival in a nurse-like cells (NLC) co-culture assay. In this model, ibrutinib treatment significantly decreased the levels of CCL3 and CCL4 and inhibited chemotaxis towards CXCL12 and CXCL13. In an adoptive transfer TCL1 mouse model, ibrutinib treatment delayed CLL progression.[49] Ibrutinib has impressive monotherapy activity in patients with relapsed CLL. Byrd et al. reported an ORR of 71% with ibrutinib in the relapsed setting.[50,51] However, most of the responses with ibrutinib are partial responses. The 30-month PFS was reported as 68.4%, with median PFS of 28.1 months in patients with del(17p) (O'Brien et al. ASCO 2014). Ibrutinib is approved by the FDA for patients with CLL who received at least one prior therapy and in patients with del(17p). Ibrutinib is well tolerated with diarrhea being the most common adverse event (mostly grade 1-2).[52]

2.6 Rationale for nivolumab and ibrutinib

There is a strong scientific rationale for targeting BTK in CLL and ibrutinib is approved by the FDA for treatment of patients with relapsed or refractory CLL and untreated patients with del(17p). There is also a strong rationale for targeting immune checkpoint inhibitors in CLL (see section 2.3). Several lines of argument support the combination of nivolumab and ibrutinib for patients with CLL. (A)

Nivolumab and ibrutinib have different mechanisms of action – Nivolumab targets PD1 leading to T cell immune responses, whereas ibrutinib targets the BTK which impacts the downstream B cell receptor pathway. (B) Early preclinical data indicate that ibrutinib may lead to increased PD-1 expression on T cells (S. Neelapu, MDACC, unpublished data). Therefore, PD-1 down regulation with nivolumab may be synergistic. (C) Ibrutinib is very well tolerated with diarrhea being the most common adverse event. Immune side-effects are not known to occur with ibrutinib. Therefore, we do not anticipate any excess toxicity with this combination.

Richter Transformation Cohort (Cohort 3): RT occurs in 5-10% of patients with CLL (Jain N, Keating M. Expert Rev Hematol. 2016 Aug;9(8):793-801). There is no standard of care for patients with RT. Majority patients are treated with chemoimmunotherapy such as OFAR, Hyper-CVAD. However, the response rate is only 40% (majority PR), and median survival is less than 1 year. There is urgent need to develop better therapies for this group of patients. Ding et al. reported 7 patients with RT who received pembrolizumab (PD1 monoclonal ab) (ASH 2015). One patient achieved CR, 2 PR (CR for large cell component), and 3 stable disease. We have treated 4 patients with RT and 1 patient with accelerated CLL. One is too early for response assessment. Of the remaining 4, 2 have achieved PR (ongoing for 7+ and 9+ months).

3.0 STUDY POPULATION

3.1 Inclusion Criteria

1. Patients will have a diagnosis of CLL or SLL, refractory to and/or relapsed after at least one prior standard therapy or untreated with del(17p) by FISH (high-risk cytogenetics) and have an indication for treatment by IWCLL 2008 criteria[53] (Cohort 1) OR have been on ibrutinib for at least 9 months with measurable persistent disease (ALC > 4K/uL, any lymph node > 1.5 cm by CT scan, or > 30% lymphocytes on bone marrow aspirate differential) (Cohort 2) OR Patients will have a diagnosis of RT, refractory to and/or relapsed after at least one prior standard therapy or untreated with del(17p) by FISH (high-risk cytogenetics) (Cohort 3)
2. Age 18 years or older
3. Eastern Cooperative Oncology Group (ECOG) Performance Status ≤2
4. Patients must have adequate renal and hepatic function
   - Total bilirubin ≤1.5 x upper limit of normal (ULN). For patients with Gilbert's disease, total bilirubin up to ≤3 x ULN is allowed provided normal direct bilirubin.
   - Serum creatinine ≤1.5 x ULN
   - ALT and AST ≤3 x ULN
5. Females of childbearing potential must have a negative serum or urine beta human chorionic gonadotrophin (β-hCG) pregnancy test result within 24 hours prior to the first dose of treatment and must agree to use an effective contraception method during the study and for 23 weeks following the last dose of the study drugs. Females of non- childbearing potential are those who are postmenopausal greater than 1 year or who have had a bilateral tubal ligation or hysterectomy. Males who have partners of childbearing potential must agree to use an effective contraceptive method during the study and for 31 weeks following the last dose of study drugs
6. Patients or their legally authorized representative must provide written informed consent.

3.2 Exclusion Criteria

1. History of another primary invasive malignancy that has not been definitively treated or in remission for at least 2 years. Patients with non-melanoma skin cancers or with carcinomas in situ are eligible regardless of the time from diagnosis (including concomitant diagnoses). If patients have another malignancy that was treated within the last 2 years, such patients may be enrolled if the likelihood of requiring systemic therapy for this other malignancy within 2 years is less than 10%, as determined by an expert in that particular malignancy at MD Anderson Cancer Center and after consultation with the Principal Investigator
2. Any major surgery, radiotherapy, cytotoxic chemotherapy, biologic therapy, immunotherapy, immunomodulatory drugs, experimental therapy within 4 weeks prior to the first dose of the study drugs. Note: Prior therapy with anti CD20 monoclonal antibody, anti CD52 monoclonal antibody, and lenalidomide are allowed. For oral targeted therapies (such as idelalisib, venetoclax), a washout of 3 days is allowed.
3. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 2 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification.
4. History of stroke or cerebral hemorrhage within 2 month.
5. Patients who have uncontrolled hypertension (defined as sustained systolic blood pressure ≥ 160 mmHg or diastolic ≥ 100 mmHg)
6. Known evidence of active cerebral/meningeal CLL. Patients may have history of CNS leukemic involvement if definitively treated with prior therapy and no evidence of active disease at the time of registration.
7. Active, uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia requiring steroid therapy.
8. Patients with autoimmune diseases are excluded: Patients with a history of Inflammatory Bowel Disease (including Crohn's disease and ulcerative colitis) are excluded from this study as are patients with a history of autoimmune disease (e.g., rheumatoid arthritis, systemic progressive sclerosis, systemic lupus erythematosus, Wegener's granulomatosis).
9. Patients with previous allogeneic stem cell transplant (SCT) within 6 months or with active acute or chronic graft-versus host disease are excluded. Patients must be off immunosuppression for GVHD for at least 30 days before cycle 1 day 1.
10. Patients with organ allografts (such as renal transplant) are excluded.
11. History of interstitial lung disease or pneumonitis.
12. Patients who are on high dose steroids (>10mg daily of prednisone or equivalent) or immune suppression medications. Note: Patients on high-dose steroids (doses >10mg/day of prednisone or equivalent) or immune suppression medications are eligible provided these drugs are discontinued at least 3 days prior to starting on the study drugs.
13. Patients with uncontrolled active infection (viral, bacterial, and fungal) are not eligible.
14. Current or chronic hepatitis B or C infection, or known seropositivity for HIV.
15. Patient is pregnant or breast-feeding.
16. Concurrent use of investigational therapeutic agent.
17. Malabsorption syndrome or other condition that precludes enteral route of administration.

18. Concomitant use of warfarin or other Vitamin K antagonists.
19. Requires treatment with a strong cytochrome P450 (CYP) 3A inhibitor (see Appendix 2).
20. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that in the opinion of the investigator may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and/or would make the patient inappropriate for enrollment into this study.

4.0 TREATMENT PLAN

4.1 Study Design

This is a phase II open label single-arm study to evaluate the combination of nivolumab and ibrutinib in patients with CLL.

COHORT 1 and 3	**C1D1**	**C1D15**	**C2D1**	**C2D15**	**C3D1 and then Q2 weeks for a total of 96 weeks**	**After 96 weeks**
Nivolumab*	3 mg/kg IV	3 mg/kg IV	3 mg/kg IV	3 mg/kg IV	3 mg/kg IV	—
Ibrutinib	—	—	Begin 420 mg orally once daily			
COHORT 2						
Nivolumab*	3 mg/kg IV	3 mg/kg IV	3 mg/kg IV	3 mg/kg IV	3 mg/kg IV	—
Ibrutinib	On ibrutinib stable oral daily dose for >9 months with residual CLL (PR) at enrollment, continue at same ibrutinib daily dose					

* **Note: After 3 cycles of treatment, the frequency of nivolumab administration may be decreased to once every 4 weeks, in consultation with the study PI.**

Each cycle is 28 days. Nivolumab dosing may be delayed for up to 3 days to accommodate for holidays/patient travel. Patients will receive nivolumab (3mg/kg IV over approximately 1 hour) monotherapy for the first cycle to assess for monotherapy toxicities of nivolumab. Nivolumab will continue for up to 24 cycles (96 weeks; 48 infusions). For Cohort 1 and cohort 3, ibrutinib will be initiated from the start of course 2. Treatment with ibrutinib will continue until disease progression, study termination, or a patient experiences a toxicity that requires discontinuation of ibrutinib. For Cohort 2, patients will have been on ibrutinib for >9 months, and ibrutinib dosing should continue. Nivolumab will be initiated after consent is provided, eligibility confirmed, and all pretreatment studies are complete. For patients with RT – ibrutinib may be introduced earlier than start of cycle 2, in case of worsening disease, after discussion with study PI.

5.0 STUDY MEDICATIONS

5.1 Nivolumab (Anti-PD1)

Nivolumab is a fully human, IgG4 (kappa) isotype, monoclonal antibody that binds PD-1. Nivolumab will be supplied in vials of 100 mg (10 mg/mL) and packaged in an open-label fashion. See Appendix 1 for Pharmacy Reference Material.

5.1.1 Preparation and Dispensing of Nivolumab

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the Investigator Brochure. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately.

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (e.g. required diluents, administration sets).

Nivolumab vials must be stored at a temperature of 2°C to 8°C and should be protected from light. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

For details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the Investigator Brochure section for “Recommended Storage and Use Conditions”. Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between nivolumab and polyolefin bags have been observed.

Nivolumab is to be administered as an IV infusion over approximately 1 hour, using a volumetric pump with a 0.2/0.22 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline for delivery but the total drug concentration of the solution cannot be below 1 mg/ml. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

Unused or expired nivolumab vials will be disposed per MDACC guidelines.

5.1.2 Administration of Nivolumab

Patients will receive nivolumab as an IV infusion over approximately 1 hour. Dosing calculations should be based on the body weight assessed at the start of each cycle as described above. If the subject’s weight on the day of dosing differs by > 10% from the weight used to calculate the original dose, the dose must be recalculated. All doses should be rounded to the nearest milligram. No doses of nivolumab may be given within 11 days of another.

5.1.3 Patient Monitoring During Infusion

For first dose, patient vital signs should be monitored prior to dosing, about 15 minutes after initiation

of the infusion (then every 15-20 minutes as indicated) and at 30 minutes after completion of the infusion, or longer if indicated, until the vital signs normalize or return to baseline. For subsequent infusions, vital signs should be collected prior to dosing and every 30 minutes during dosing.

5.1.4 Treatment of Nivolumab Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. Infusion reactions should be graded according to NCI CTCAE (version 4.0) guidelines.

Treatment recommendations for nivolumab related infusion reactions are provided below and may be modified based on MD Anderson treatment standards and guidelines, as appropriate:

For Grade 1 symptoms (Mild reaction; infusion interruption not indicated; intervention not indicated): Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g. antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours):

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the case report form (CRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms [Severe reaction, Grade 3: prolonged (i.e. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g. renal impairment, pulmonary infiltrates), Grade 4: life- threatening; pressor or ventilatory support indicated]:

Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and treat the

subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Institutional guidelines will be followed for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (e.g. appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g. oral antihistamine or corticosteroids).

5.2 Ibrutinib

Ibrutinib is a small-molecule inhibitor of BTK. Ibrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. Ibrutinib 420 mg will be administered orally once daily. Ibrutinib should be administered with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and patients should not attempt to open capsules or dissolve them in water. Each dose of ibrutinib should be taken approximately 2 hours after a meal or at least 30 minutes before the next meal, at approximately the same time each day. If a dose of ibrutinib is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. Extra capsules of ibrutinib should not be taken to make up for the missed dose.

Concomitant use of strong CYP3A inhibitors which would be taken chronically (e.g., ritonavir, indinavir, nelfinavir, saquinavir, boceprevir, telaprevir, nefazodone) is not recommended. Concomitant use of strong CYP3A inducers (e.g., rifampin, rifabutin, phenytoin, carbamazepine, and St. John's Wort) are not recommended. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A. Please see Section 6.2 for more details.

5.2.1 How Supplied

Supplied as 140mg capsules

5.2.2 Stability

Store bottles at room temperature 20°C to 25°C

5.2.3 Pharmacokinetics

Absorption: Ibrutinib is absorbed after oral administration with a median Tmax of 1 to 2 hours. Ibrutinib exposure increases with doses up to 840 mg. The steady-state AUC (mean ± standard deviation) in patients at 420 mg is 680 ± 517 ng·h/mL. Administration with food increased ibrutinib AUC by approximately 2-fold.

Distribution: Reversible binding of ibrutinib to human plasma protein in vitro was 97.3%.

Metabolism: Metabolism is the main route of elimination for ibrutinib. It is metabolized to several metabolites primarily by cytochrome P450, CYP3A, and to a minor extent by CYP2D6. The active metabolite, PCI-45227, is a dihydrodiol metabolite with inhibitory activity towards BTK approximately 15 times lower than that of ibrutinib.

Elimination: The half-life of ibrutinib is 4 to 6 hours. Ibrutinib, mainly in the form of metabolites, is

eliminated primarily via feces.

Renal Impairment: Ibrutinib is not significantly cleared renally; urinary excretion of metabolites is < 10% of the dose. Creatinine clearance > 25 mL/min had no influence on the exposure to ibrutinib. There are no data in patients with severe renal impairment (creatinine clearance < 25 mL/min) or in patients on dialysis.

Hepatic Impairment: Ibrutinib is metabolized in the liver. No clinical trials have been completed in patients with impaired hepatic function.

6.0 DOSE DELAYS AND MODIFICATIONS

Patients who experience Grade 3 or 4 toxicity that can be clearly attributed to either nivolumab or to ibrutinib may continue treatment with the other agent while the causative agent is delayed until resolution of toxicity to grade ≤1 or baseline. In cases where Grade 3 or 4 toxicity cannot be attributed to a specific study drug, both study drugs should be held regardless of attribution of toxicity until the toxicity is resolved to grade ≤1 or baseline. Grade 3 or 4 nivolumab immune-related toxicities will generally result in discontinuation of nivolumab, leaving ibrutinib monotherapy.

6.1 Dose modification for nivolumab

Dose reductions or dose escalations are not permitted.

6.1.1 Pulmonary adverse events

Pulmonary AEs have been observed following treatment with nivolumab and have occurred after a single dose and after as many as 48 treatments. The majority of cases reported were Grade 1 or Grade 2 and patients presented with either asymptomatic radiographic changes (eg, focal ground glass opacities, patchy infiltrates) or with symptoms of dyspnea, cough, or fever. Early recognition and treatment of pneumonitis is critical to its management. Patients should be advised to seek medical evaluation promptly if they develop new onset dyspnea, cough or fever or if they have worsening of these baseline symptoms. As respiratory symptoms are common in patients with CLL, it is important that an evaluation/work-up distinguish between non-drug-related causes (eg, infection, progression of disease) and a possible drug-related pulmonary toxicity as the management of these events is quite different. Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue therapy.

Grade of Pneumonitis	Management	Follow-up
Grade 1 (Asymptomatic; clinical or diagnostic observations only; intervention not indicated)	▪ Consider delay of nivolumab ▪ Monitor for symptoms every 2-3 days ▪ Consider Pulmonary and ID consults	▪ Re-image at least every 3 weeks. If worsens: ▪ Treat as Grade 2 or 3-4
Grade 2 (Symptomatic; medical intervention indicated; limiting instrumental ADL)	▪ Delay nivolumab ▪ Pulmonary and ID consults ▪ Monitor symptoms daily, consider hospitalization ▪ Steroids: 1 mg/kg/day	▪ Re-image every 1-3 days If improves: ▪ When symptoms return to near baseline, taper steroids over at least 1 month and then resume nivolumab

	methyl-prednisolone IV or oral equivalent ▪ Consider bronchoscopy, lung biopsy	<u>If not improving after 2 weeks or worsening:</u> ▪ Treat as Grade 3-4
Grade 3 (Severe symptoms; limiting self-care ADL; oxygen indicated) or Grade 4 (Life-threatening respiratory compromise; urgent intervention indicated [e.g., tracheotomy or intubation])	▪ Discontinue Nivolumab ▪ Hospitalize ▪ Pulmonary and ID consults ▪ Steroids: 2-4 mg/kg/day methylprednisolone IV or IV equivalent ▪ Add prophylactic antibiotics for opportunistic infections ▪ Consider bronchoscopy, lung biopsy	<u>If improves to baseline:</u> ▪ Taper steroids over at least 6 weeks <u>If not improving after 48 hours or worsening:</u> ▪ Add additional immunosuppression (e.g. infliximab, cyclophosphamide, IVIG, or mycophenolate mofetil)

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed.

6.1.2 Gastrointestinal adverse events

Gastrointestinal AEs have been observed following treatment with nivolumab. Most cases of diarrhea were low grade (Grade 1-2). Colitis occurs less frequently than diarrhea. High grade cases of diarrhea and colitis were managed with corticosteroids and in all cases the events resolved. Early recognition and treatment of diarrhea and colitis are critical to its management. Patients should be advised to seek medical evaluation if they develop new onset diarrhea, blood in stool, or severe abdominal pain, or if they have worsening of baseline diarrhea. As GI symptoms are common in patients with CLL, it is important that an evaluation/work-up distinguish between non-drug-related causes (eg, infection, progression of disease) and a possible drug-related AE as the management is quite different. Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue nivolumab therapy. Opiates/narcotics may mask symptoms of perforation. NOTE: As diarrhea could occur from the use of ibrutinib, patients with grade 2 diarrhea should have their ibrutinib held as well.

Grade of Diarrhea/Colitis	**Management**	**Follow-up**
Grade 1 **Diarrhea (Increase of <4 stools per day over baseline)** **Colitis (Asymptomatic)**	▪ Continue nivolumab ▪ Symptomatic treatment	▪ Close monitoring for worsening symptoms <u>If worsens:</u> ▪ Treat as Grade 2 or 3-4
Grade 2 **Diarrhea (Increase of 4 - 6 stools per day over baseline)** **Colitis (Abdominal pain; blood in stool)**	▪ Delay nivolumab ▪ Symptomatic treatment	<u>If improves to grade 1:</u> ▪ Resume nivolumab <u>If persists > 5-7 days or recur:</u> ▪ Steroids: 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent ▪ When symptoms improve to grade 1, taper steroids over

		at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume nivolumab If worsens or persists > 3-5 days with oral steroids: ▪ Treat as Grade 3/4
Grade 3 **Diarrhea (Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; interfering with ADL)** **Colitis (Severe abdominal pain; medical intervention indicated; peritoneal signs)** **Grade 4** **Diarrhea (Life-threatening consequences; urgent intervention indicated)** **Colitis (Life-threatening consequences; urgent intervention indicated; perforation)**	▪ Discontinue Nivolumab ▪ Steroids: 1-2 mg/kg/day methylprednisolone IV or IV equivalent ▪ Add prophylactic antibiotics for opportunistic infections ▪ Consider sigmoidoscopy or colonoscopy	If improves: ▪ Continue steroids until grade 1, then taper over at least 1 month If persists >3-5 days, or recurs after improvement: ▪ Add infliximab (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed.

6.1.3 Hepatic adverse events

Hepatic AEs including elevated liver function tests (LFTs) and infrequently hepatitis have been observed following treatment with nivolumab. Most cases were low or moderate grade. Higher grade hepatic AEs were managed with corticosteroids and in all cases the events resolved. Early recognition and treatment of elevated LFTs and hepatitis are critical to its management. Patients should be advised to seek medical evaluation if they notice jaundice (yellow appearance of skin or sclera) or if they develop bruising, bleeding, or right-sided abdominal pain. Physicians should monitor LFTs prior to each nivolumab treatment. As LFT abnormalities are common in patients with CLL, it is important that an evaluation/work-up distinguish between non-drug-related causes (eg, infection, progression of disease, concomitant medications, alcohol) and a possible drug- related AE as the management is quite different. If non-inflammatory cause is identified, treat accordingly and continue nivolumab therapy. Consider imaging for obstruction.

Grade of LFT abnormality	Management	Follow-up
Grade 1 **AST or ALT > ULN - 2.5 x ULN** **and/or T. bili > ULN - 1.5 x ULN**	▪ Continue nivolumab	▪ Continue LFT monitoring per protocol If worsens: ▪ Treat as Grade 2 or 3-4
Grade 2 **AST or ALT > 2.5 to ≤ 5 x ULN**	▪ Delay nivolumab (Note: Discontinue nivolumab if	If returns to baseline: ▪ Resume routine monitoring,

and/or T. bili > 1.5 to ≤ 3 x ULN	concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN) ▪ Monitor LFTs at least every 3 days	resume nivolumab If elevations persist > 5-7 days or worsen: ▪ Steroids: 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, and resume nivolumab ▪ consider prophylactic antibiotics for opportunistic infections
Grade 3-4 **AST or ALT > 5 x ULN** **and /or T.bili >3 x ULN**	▪ Discontinue Nivolumab (Note: Nivolumab may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN) ▪ Monitor LFTs every 1-2 days ▪ Steroids: 1-2 mg/kg/day methylprednisolone IV or IV equivalent (Note: Use 2 mg/kg/day dose for Grade 4 LFTs) methylprednisolone IV. ▪ Add prophylactic antibiotics for opportunistic infections ▪ Consult hepatologist or gastroenterologist	If returns to grade 2: ▪ Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: ▪ Add mycophenolate mofetil ▪ If no response within an additional 3-5 days, consider other immunosuppressants

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed.

6.1.4 Endocrine adverse events

Endocrinopathies have been observed following treatment with nivolumab. Most cases are low or moderate grade. The events have typically been identified through either routine periodic monitoring of specific laboratories (eg, TSH) or as part of a work-up for associated symptoms (eg, fatigue). Events may occur within weeks of beginning treatment but also have been noted to occur after many months (while still on treatment). More than one endocrine organ may be involved. Early recognition and treatment of endocrinopathies are critical to its management. Patients should be advised to seek medical evaluation if they notice new onset of fatigue, lightheadedness, or difficulty with vision or if baseline fatigue worsens. As fatigue is common in patients with CLL, it is important that an evaluation/work-up distinguish between non-drug- related causes (eg, progression of disease, anemia, concomitant medications, depression) and a possible drug-related AE as the management is quite different. The principal management of endocrinopathies is hormone replacement therapy.

Asymptomatic TSH elevation	▪ Continue nivolumab ▪ If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: consider endocrinology consult	
Symptomatic endocrinopathy	▪ Evaluate endocrine function ▪ Consider pituitary scan <u>Symptomatic with abnormal lab/pituitary scan:</u> ▪ Delay nivolumab ▪ Steroids: 1-2 mg/kg/day methylprednisolone IV or PO equivalent ▪ Initiate appropriate hormone therapy <u>No abnormal lab/pituitary MRI scan but symptoms persist:</u> ▪ Repeat labs in 1-3 weeks / MRI in 1 month	<u>If improves (with or without hormone replacement):</u> ▪ Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections ▪ Resume nivolumab ▪ Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (e.g. severe dehydration, hypotension, shock out of proportion to current illness)	▪ Delay or discontinue nivolumab ▪ Rule out sepsis ▪ Stress dose of IV steroids with mineralocorticoid activity ▪ IV fluids ▪ Consult endocrinologist ▪ If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy	

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed.

6.1.5 Skin adverse events

Rash and pruritus are the most common skin AEs observed following treatment with nivolumab. The rash is typically focal with a maculopapular appearance occurring on the trunk, back, or extremities. Most cases have been low or moderate grade. In some cases, rash and pruritus resolved without intervention. Topical corticosteroids have been used for some cases of rash. Anti-histamines have been used for some cases of pruritus. More severe cases responded to systemic corticosteroids. Patients should be advised to seek medical evaluation if they notice new onset rash. Early consultation with a dermatology specialist and a biopsy should be considered if there is uncertainty as to the cause of the rash or if there is any unusual appearance or clinical feature associated with it. Other drugs which may cause rash should be considered in the differential and if possible discontinued.

Grade of Rash	Management	Follow-up
Grade 1-2 **(Covering ≤ 30% of BSA)**	▪ Continue nivolumab ▪ Symptomatic therapy	<u>If persists > 1-2 weeks or recurs:</u> ▪ Consider skin biopsy

	(e.g. antihistamines, topical steroids)	▪ Delay nivolumab ▪ Steroids: Consider 0.5-1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving , taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume nivolumab <u>If worsens:</u> ▪ Treat as Grade 2 or 3-4
Grade 3-4 (Covering >30% BSA; Life threatening consequences)	▪ Delay or discontinue nivolumab ▪ Consider skin biopsy ▪ Dermatology consult ▪ Steroids: 1-2 mg/kg/day IV methylprednisolone ▪ IV or IV equivalent	<u>If improves to Grade 1:</u> ▪ Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections ▪ Resume nivolumab

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed.

6.1.6 Renal adverse events

Elevated creatinine and biopsy confirmed tubulointerstitial nephritis and allergic nephritis have been infrequently observed following treatment with nivolumab. Most cases were Grade 2 or Grade 3 and based on creatinine elevation. Events were managed with corticosteroids and in all cases renal function partially or fully improved. As creatinine abnormalities are common in patients with CLL and other comorbidities, it is important that an evaluation/work-up distinguish between non- drug-related causes (eg, dehydration, concomitant medications, hypotension, progression of disease) and a possible drug-related AE as the management is quite different. The principal treatment for renal AEs is corticosteroids.

Grade of Creatinine Elevation	Management	Follow-up
Grade 1 (Creatinine > ULN and > than baseline but ≤ 1.5x baseline)	▪ Continue nivolumab ▪ Monitor creatinine weekly	<u>If returns to baseline:</u> ▪ Resume routine creatinine monitoring per protocol <u>If worsens:</u> ▪ Treat as Grade 2 or 3-4
Grade 2-3 (Creatinine > 1.5x baseline to ≤ 6x ULN)	▪ Delay nivolumab ▪ Monitor creatinine every 2-3 days ▪ Steroids: 0.5-1 mg/kg/day methyl-prednisolone IV or oral equivalent ▪ Consider renal biopsy	<u>If returns to Grade 1:</u> ▪ Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume nivolumab and routine creatinine monitoring per protocol

		If elevations persist >7 days or worsen: ▪ Treat as Grade 4
Grade 4 (Creatinine > 6x ULN)	▪ Discontinue Nivolumab ▪ Monitor creatinine daily ▪ Steroids: 1-2 mg/kg/day methylprednisolone IV or IV equivalent ▪ Consult nephrologist ▪ Consider renal biopsy	If returns to Grade 1: ▪ Taper steroids over at least 1 month add prophylactic antibiotics for opportunistic infections

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed.

6.1.7 Neurologic adverse events

Neurologic AEs have been uncommonly observed following treatment with nivolumab. Neurologic AEs can manifest as central abnormalities (eg, aseptic meningitis, encephalitis) or peripheral sensory/motor neuropathies (eg, Guillain-Barre Syndrome). Early recognition and treatment of neurologic AEs is critical to its management. Patients should be advised to seek medical evaluation if they notice impairment in motor function (eg, weakness), changes in sensation (eg, numbness), or symptoms suggestive of possible central nervous system abnormalities such as new headache or mental status changes. As neurologic symptoms can be common in patients with cancer, it is important that an evaluation/work-up distinguish between non-drug-related causes (eg, progression of disease, concomitant medications, infection) and a possible drug-related AE as the management is quite different.

Grade of Neurological Toxicity	Management	Follow-up
Grade 1 (Asymptomatic or mild symptoms; intervention not indicated)	▪ Continue nivolumab	▪ Continue to monitor patient If worsens: ▪ Treat as Grade 2 or 3-4
Grade 2 (Moderate symptoms; limiting instrumental ADL)	▪ Delay nivolumab ▪ Symptomatic treatment ▪ Steroids: 0.5-1 mg/kg/day methyl-prednisolone IV or oral equivalent	If improves to baseline: ▪ Resume nivolumab If worsens: ▪ Treat as Grade 3-4
Grade 3-4 (Severe symptoms; limiting self-care ADL; life-threatening)	▪ Discontinue Nivolumab ▪ Neurology consult ▪ Symptomatic treatment ▪ Steroids: 1-2 mg/kg/day methylprednisolone IV or IV equivalent ▪ Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: ▪ Taper steroids over at least 1 month If worsens or atypical presentation: ▪ Consider IVIG or other immunosuppressive therapies

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed.

6.1.8 Lipase/Amylase Elevations

Asymptomatic elevations in lipase and amylase have been reported. In monotherapy studies of nivolumab, lipase and amylase levels were not systematically monitored, so an estimate of the frequency of asymptomatic lipase/amylase elevations is unknown. In a study evaluating the safety of the nivolumab + ipilimumab combination in melanoma, lipase and amylase levels were systematically monitored and the frequency of any grade lipase/amylase AEs was 29% and Grade 3-4 were 18%. Very few patients reported associated symptoms (eg, abdominal pain) or radiographic findings (eg, stranding) consistent with pancreatitis. Thus, there does not seem to be clinical significance to the elevated laboratory values. As lipase/amylase abnormalities are not uncommon in patients with cancer, it is important that an evaluation/work-up distinguish between non-drug-related causes (eg, progression of disease, concomitant medications, alcohol) and a possible drug-related cause as the management is quite different. The recommended management of nivolumab-related elevated lipase/amylase values centers around close observation. Physicians should ensure patients have no associated symptoms consistent with pancreatitis such as abdominal pain. Corticosteroids do not seem to alter the natural history of lipase/amylase elevations. Laboratory values tend to fluctuate day to day and eventually return to baseline or low grade over the course of weeks whether or not patients receive corticosteroids. Asymptomatic elevations should be monitored approximately weekly. For patients with elevated lipase/amylase and symptoms consistent with possible pancreatitis, nivolumab should be discontinued and consultation with a gastroenterologist should be considered.

6.1.9 Uveitis and Visual Complaints

Immune therapies have been uncommonly associated with visual complaints. Inflammation of components within the eye (eg, uveitis) is an uncommon but clinically important event. An ophthalmologist should evaluate visual complaints. Topical corticosteroids may be used to manage low grade events. Low-grade events that do not resolve and high-grade events should be managed with systemic corticosteroids.

6.1.10 Nivolumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related AE, with the following exceptions:
    - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, drug-related AE
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, leukopenia, AST, ALT, total bilirubin, or asymptomatic amylase or lipase:
    - Grade 3 lymphopenia or leukopenia does not require dose delay
    - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
    - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity
    - Asymptomatic amylase or lipase does not require dose delay

- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication

6.1.11 Criteria to Resume Treatment

Patients may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤1 or baseline value, with the following exceptions:

- Patients may resume treatment in the presence of Grade 2 fatigue
- Patients who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Patients with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin
- Patients with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Discontinuation Section, Section 12.0) should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled timepoint per protocol. However, if the treatment is delayed past the next scheduled timepoint per protocol, the next scheduled timepoint will be delayed until dosing resumes.

If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in discontinuation section.

6.2 Dose modifications for ibrutinib

Interrupt ibrutinib for any Grade 3 or greater non-hematological, Grade 3 or greater neutropenia with infection or fever, or Grade 4 hematological toxicities. Once the symptoms of the toxicity have resolved to Grade 1 or baseline, reinitiate ibrutinib at the starting dose. If the toxicity reoccurs, reduce dose by one capsule (140 mg per day).
NOTE: As diarrhea could occur from the use of ibrutinib or nivolumab, patients with grade 2 diarrhea should have their ibrutinib held.

Recommended dose modifications are described below:

Toxicity Occurrence	**Dose modification** **Starting Dose = 420 mg daily**
First	Restart at 420 mg daily
Second	Restart at 280 mg daily
Third	Restart at 140 mg daily
Fourth	Discontinue ibrutinib

Dose Modifications for Use with CYP3A Inhibitors/Inducers: Ibrutinib is metabolized primarily by CYP3A. Concomitant use of strong CYP3A inhibitors which would be taken chronically (e.g., ritonavir, indinavir, nelfinavir, saquinavir, boceprevir, telaprevir, nefazodone) is not recommended. For strong CYP3A inhibitors used short-term (e.g., antifungals and antibiotics for 7 days or less, e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin), consider holding ibrutinib therapy during the duration of the inhibitor use. Avoid strong CYP3A inhibitors that are needed chronically. If a moderate CYP3A inhibitor must be used (e.g., fluconazole, darunavir, erythromycin, diltiazem, atazanavir, aprepitant, amprenavir, fosamprevir, verapamil, grapefruit products and ciprofloxacin), reduce ibrutinib dose to 140 mg daily.
Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A. Avoid Star fruit as it contains inhibitors of CYP3A.
Administration of ibrutinib with strong inducers of CYP3A can decrease ibrutinib plasma concentrations. Concomitant use of strong CYP3A inducers (e.g., rifampin, rifabutin, phenytoin, carbamazepine, and St. John's Wort) are not recommended.

A list of common CYP3A inhibitors and inducers is provided in Appendix 2; a comprehensive list of inhibitors, inducers, and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/table.aspx. This website is continually revised and should be checked frequently for updates.

7.0 CONCOMITANT THERAPY

7.1 Allowed concomitant therapy

Patients should receive full supportive care during study participation, including hematopoietic growth factors, transfusion of blood products, fluid and electrolyte replacement, and antibiotics when appropriate.

7.2 Excluded concomitant therapy

Use of the following therapies is prohibited during the study:

- Cytotoxic chemotherapy
- Immunotherapy (outside of this study)
- Radiotherapy (Note: Localized radiotherapy to an area not compromising bone marrow function is allowed)
- Any therapies intended for the treatment of lymphoma/leukemia whether FDA-approved or experimental (outside of this study)
- Steroid therapy for anti-neoplastic intent. Inhaled steroids for asthma, topical steroids, steroids as part of premedication for nivolumab, or replacement/stress corticosteroids are permitted.
- Strong CYP3A inhibitors which would be taken chronically
- Grapefruit, Seville oranges, Star fruit
- Strong CYP3A inducers (e.g., rifampin, rifabutin, phenytoin, carbamazepine, and St. John's Wort) are not recommended

8.0 PRETREATMENT EVALUATIONS

1. Pretreatment evaluation will include a complete history and physical examination including vital signs, neurological examination, ECOG performance status, height and weight and recording of concurrent medications (within 14 days of the first dose)
2. Complete blood count (hemoglobin, white blood cell count, platelet count, white blood count differential) (within 14 days of the first dose)
3. Clinical laboratory evaluation will include serum sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH, amylase, lipase, β-2 microglobulin, immunoglobulins (within 14 days of the first dose)
4. B, T, NK cell counts and subset analyses on the peripheral blood (within 14 days of the first dose)
5. PT, aPTT (within 14 days of the first dose)
6. Urinalysis (within 14 days of the first dose)
7. HIV Ab, Hepatitis C ab, HBsAg, anti-HBcAb (within 30 days of the first dose)
8. TSH, Free T4 (within 30 days of the first dose)
9. Women of childbearing potential must have a negative serum or urine β-hCG pregnancy test result within 24 hours prior to the first dose.
10. 12-lead EKG (within 30 days of the first dose)
11. MUGA or Echocardiogram (within 30 days of the first dose)
12. Bone marrow aspiration and biopsy (within 60 days of the first dose if no intervening treatment for CLL given)
13. CT scan of the neck (if indicated), chest, abdomen, and pelvis with IV and oral contrast, within 30 days of the first dose with no intervening treatment for CLL given. Patients with palpable cervical lymphadenopathy noted at screening physical examinations should have imaging of the neck included in their screening imaging studies and at subsequent time points for response assessment. Note: PET scan may be used instead of the CT scan imaging.

9.0 EVALUATIONS DURING THE STUDY

Cycle 1 Day 1

1. CBC, platelet count and differential; serum sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH (Note: Cycle 1 Day 1 labs obtained within 3 days prior to the Day 1 is acceptable)
2. Vital signs, history and physical examination including neurological examination (Note: History and physical examination within 3 days prior to the Day 1 is acceptable)

Cycle 1 Day 8 (+/- 3 days)

1. CBC, platelet count and differential; serum sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH
2. Vital signs, history and physical examination including neurological examination

Cycle 1 Day 15 (+/- 3 days)

1. CBC, platelet count and differential; serum sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH, amylase, lipase
2. Vital signs, history and physical examination including neurological examination
3. Urinalysis

Cycle 1 Day 22 (+/- 3 days)
1. CBC, platelet count and differential; serum sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH
2. Vital signs, history and physical examination including neurological examination

End of Cycle 1 (+/- 3 days)
1. For COHORT 1 only - CT scan of the neck (if indicated), chest, abdomen, and pelvis with IV and oral contrast. PET scan may be used instead of the CT scan imaging. Note: This evaluation should be done prior to starting ibrutinib in this cohort (i.e. prior to starting cycle 2).
2. For COHORT 1 only – Bone marrow aspiration with multi-color flow cytometry for MRD evaluation.

Cycle 2 Day 1 (+/- 3 days)
1. CBC, platelet count and differential; serum sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH, amylase, lipase, quantitative immunoglobulin levels, and B, T, NK cell counts and subset analyses on the peripheral blood
2. Vital signs, history and physical examination including neurological examination
3. TSH, Free T4
4. Urinalysis

Cycle 2 Day 8 (+/- 3 days)
1. CBC, platelet count and differential; serum sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH

Cycle 2 Day 15 (+/- 3 days)
1. CBC, platelet count and differential; serum sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH, amylase, lipase
2. Serum or urine β-hCG pregnancy test (for women of childbearing potential)
3. Vital signs, history and physical examination including neurological examination

Cycle 2 Day 22 (+/- 3 days)
1. CBC, platelet count and differential; serum sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH

Cycle 3 Day 1 (+/- 3 days)

1. CBC, platelet count and differential; serum sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH, amylase, lipase, quantitative immunoglobulin levels and B, T, NK cell counts and subset analyses on the peripheral blood
2. Vital signs, history and physical examination including neurological examination
3. TSH, Free T4
4. Urinalysis

Cycle 3 Day 8 (+/- 3 days)

1. CBC, platelet count and differential; serum sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH

Cycle 3 Day 15 (+/- 3 days)

1. CBC, platelet count and differential; serum sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH, amylase, lipase
2. Vital signs, history and physical examination including neurological examination

Cycle 3 Day 22 (+/- 3 days)

1. CBC, platelet count and differential; serum sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH

End of Cycle 3 (+/- 1 week)

1. Bone marrow aspiration and biopsy with multi-color flow cytometry for MRD evaluation.
2. CT scan of the neck (if indicated), chest, abdomen, and pelvis with IV and oral contrast. PET scan may be used instead of the CT scan imaging.

Cycle 4 Day 1 (+/- 3 days)

1. CBC, platelet count and differential; serum sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH, amylase, lipase, β-2 microglobulin, quantitative immunoglobulin levels and B, T, NK cell counts and subset analyses on the peripheral blood
2. Vital signs, history and physical examination including neurological examination
3. TSH, Free T4
4. Urinalysis
5. Serum or urine β-hCG pregnancy test (for women of childbearing potential)

Cycle 4 Day 15 (+/- 3 days)

1. CBC, platelet count and differential; serum sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH, amylase, lipase

2. Vital signs, history and physical examination including neurological examination

Cycle 5 Day 1 (+/- 3 days)

1. CBC, platelet count and differential; serum sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH, amylase, lipase, quantitative immunoglobulin levels and B, T, NK cell counts and subset analyses on the peripheral blood
2. Vital signs, history and physical examination including neurological examination

Cycle 5 Day 15 (+/- 3 days)

1. CBC, platelet count and differential; serum sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH, amylase, lipase
2. Serum or urine β-hCG pregnancy test (for women of childbearing potential)
3. Vital signs, history and physical examination including neurological examination

Cycle 6 Day 1 (+/- 3 days)

1. CBC, platelet count and differential; serum sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH, amylase, lipase, quantitative immunoglobulin levels and B, T, NK cell counts and subset analyses on the peripheral blood
2. Vital signs, history and physical examination including neurological examination

Cycle 6 Day 15 (+/- 3 days)

1. CBC, platelet count and differential; serum sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH, amylase, lipase
2. Vital signs, history and physical examination including neurological examination

End of Cycle 6 (+/- 1 week)

1. Bone marrow aspiration and biopsy with multi-color flow cytometry for MRD evaluation.
2. CT scan of the neck (if indicated), chest, abdomen, and pelvis with IV and oral contrast. PET scan may be used instead of the CT scan imaging.

Cycle 7 onwards (+/- 3 days)

1. CBC, platelet count and differential; serum sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH, amylase, lipase (on the day of Nivolumab infusions)
2. Complete history and physical examination including vital signs and neurological examination at least monthly.
3. Quantitative immunoglobulin levels every month
4. B, T, NK cell counts and subset analyses on the peripheral blood every 3 months
5. Serum or urine β-hCG pregnancy test (for women of childbearing potential) at least every 6 weeks
6. TSH, Free T4 every 3 months

7. Urinalysis every 3 months
8. Bone marrow aspiration and biopsy with multi-color flow cytometry for MRD evaluation every 3 months for the first year of the study, then every 6 months
9. CT scan of the neck (if indicated), chest, abdomen, and pelvis with IV and oral contrast every 3 months for the first year of the study, then then every 6 months. PET scan may be used instead of the CT scan imaging.

Note: Patients who complete all protocol specified nivolumab treatments (or discontinue nivolumab early, see Section 12.0) will have the following evaluations until removal from study (These are the patients continuing on ibrutinib monotherapy):

1. CBC, platelet count and differential; serum sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH at least monthly for the first 3 months, then every 3 months
2. Complete history and physical examination including vital signs and neurological examination at least monthly for the first 3 months, then every 3 months.
3. Quantitative immunoglobulin levels monthly for the first 3 months, then every 3 months
4. B, T, NK cell counts and subset analyses on the peripheral blood monthly for the first 3 months, then every 3 months
5. Serum or urine β-hCG pregnancy test (for women of childbearing potential) monthly for 3 times
6. TSH, Free T4 every 3 months
7. Urinalysis every 3 months
8. Bone marrow aspiration and biopsy with multi-color flow cytometry for MRD evaluation every 3 months for the first year of the study, then every 6 months
9. CT scan of the neck (if indicated), chest, abdomen, and pelvis with IV and oral contrast every 3 months for the first year of the study, then then every 6 months. PET scan may be used instead of the CT scan imaging.

End of Study Visit – Patients, who are taken off study for any reason, will have an end of study visit. The end of study visit will occur 30 days +/- 7 days after the last dose of the study drugs. At this visit, the patient will have labs (CBC, platelet count and differential, sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH), history and physical examination including neurological examination, serum immunoglobulins, B, T, NK cell counts and subset analyses on the peripheral blood, bone marrow aspiration and biopsy with multi-color flow cytometry for MRD evaluation (if the previous bone marrow evaluation was >3 months ago), and CT or PET imaging (if the previous CT or PET imaging was >3 months ago).

After completion of all protocol related treatments, patients will be followed for at least one year with at least monthly labs (CBC, platelet count and differential, sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH), at least monthly history and physical examination, serum immunoglobulins every 3 months, B, T, NK cell counts and subset analyses on the peripheral blood every 3 months, bone marrow aspiration and biopsy with multi-color flow cytometry for MRD evaluation every 3-6 months, and CT or PET imaging every 3-6 months. Note: This post-protocol follow-up period of one year will end early if the

patient starts another treatment for their CLL/SLL. Inability to comply with these post-protocol follow-up evaluations will not be considered a protocol-deviation.

Adverse Events Monitoring - Adverse events will be assessed continually while on the study, until 30 days after the last dose of drug

NOTE: All treatments with nivolumab must be administered at the MDACC. During the first cycle all laboratory evaluations will be done at MDACC. Subsequently, the patient may have laboratory work and physical examination done at a local clinic and the results reported to the research nurse for the study. The laboratory work done at a local clinic will be forwarded to the patient's attending physician at MDACC, or PI of the study, who will sign off on the labs to verify that the results have been reviewed.

Outside Physician Participation During Treatment

1. MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record

2. A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's care (Appendix 3)

3. Protocol required evaluations outside MDACC will be documented by fax. Faxed evaluations will be dated and signed by the MDACC physician/investigator indicating that they have reviewed it.

4. A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.

5. Documentation to be provided by the local physician will include progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.

6. The home physician will be requested to report to the MDACC physician/investigator all life threatening events within 24 hours of documented occurrence.

10.0 CRITERIA FOR RESPONSE

Response will be assessed by the investigator, based on physical examinations, CT scans, laboratory results, and bone marrow examinations, according to the modified 2008 IWCLL response criteria for CLL. OR is defined as a CR or PR (or CR with incomplete marrow recovery) as determined by investigator assessment using CLL response criteria.[53,54] Patients with missing or no response assessments will be classified as non-responders.

Complete Response (CR): Requires all of the following:

- Peripheral blood lymphocytes <4000/μL
- Absence of significant lymphadenopathy (eg, lymph nodes >1.5 cm in diameter) by physical exam and CT (PET may be used in place of CT scan)

- No hepatomegaly or splenomegaly by physical exam (and CT/PET scan if assessment was abnormal before therapy or if physical exam is inconclusive)
- Absence of constitutional symptoms
- Blood counts above the following values (without need for growth factors or transfusions): neutrophils >1,500/µL, platelets >100,000/µL, hemoglobin >11.0 g/dl
- Bone marrow aspirate and biopsy must be normocellular for age with <30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent. If the bone marrow is hypocellular, a repeat determination should be made in 4 weeks or when peripheral blood counts have recovered. Hypocellular marrow should be noted as **CR with incomplete marrow recovery (CRi)**.

Partial Response (PR): Requires one of the following for a period ≥2 months:

- ≥50% decrease in peripheral lymphocyte count from pretreatment baseline value
- ≥50% reduction in lymphadenopathy as defined by:
    - ≥50% decrease in lymph node size either in the sum products of up to 6 lymph nodes or in the largest diameter of the enlarged lymph node(s) detected before therapy
    - No increase in any lymph node and no new enlarged lymph node (In small lymph nodes [<2cm], an increase of <25% is not considered significant)
- ≥50% reduction in pretreatment enlargement of the spleen or liver, as detected by CT/PET scan

Additionally, these patients must have at least one of the following for ≥2 months:

- Neutrophils >1,500/µL (without need for growth factors)
- Platelets >100,000/µL or ≥50% improvement over baseline (without need for growth factors)
- Hemoglobin >11.0 g/dl (untransfused) or ≥50% improvement over baseline

Additionally, patients who fulfill the criteria above for CR but who have the following will be considered a PR

- Patients with bone marrow nodules (may be noted as **nodular PR**). Immunohistochemistry should be performed to define whether these nodules are composed of primarily T cells or lymphocytes other than CLL cells, or CLL cells.
- Patients with persistent anemia or thrombocytopenia or neutropenia apparently unrelated to disease activity and more likely the consequence of persistent drug toxicity (may be noted as **CRi**).

Progressive Disease (PD): Characterized by ≥1 of the following events:

- Lymphadenopathy: ≥50% increase in greatest determined diameter of any previous site; appearance of any new lesion, such as enlarged lymph nodes (>1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates (NOTE: new lesion or isolated and/or transient increase in target lesion(s) in the setting of reduced lymph node size or organomegaly, or improvement in hemoglobin/platelets is not considered PD unless persists for >4 weeks (CT/PET scan confirmation required)
- ≥50% increase in the previously noted enlargement of the liver or spleen; de novo appearance of hepatomegaly or splenomegaly

- ≥50% increase in the absolute number of circulating lymphocytes to ≥5,000/μL (NOTE: In the absence of other objective evidence of PD, lymphocytosis alone is not considered progressive disease)
- Transformation to a more aggressive histology (i.e., Richter's syndrome)
- Occurrence of cytopenia (neutropenia, anemia, or thrombocytopenia) attributable to CLL (decrease in hemoglobin ≥2 gm/dL or to <100 g/L; or decrease ≥50% in platelets or to <100,000/uL) that occurs ≥3 months after treatment, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.

Stable Disease (SD): Patients who do not fulfill the criteria for complete or partial response as defined above but do not exhibit progressive disease will be considered as having stable disease.

Responses for patients with RT will be assessed by non-Hodgkin's lymphoma (NHL) criteria.[55]

11.0 ADVERSE EVENT REPORTING

11.1 Leukemia-specific Adverse Event Recording and Reporting Guidelines
These guidelines serve to bring the Department of Leukemia in compliance with the institutional policy on Reporting of Serious Adverse Events.

Adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment. Adverse drug reaction is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.

Assessing causal connections between agents and disease is fundamental to the understanding of adverse drug reactions. In general, a drug may be considered a contributory cause of an adverse event if, had the drug not been administered, 1) the event would not have happened at all, 2) the event would have occurred later than it actually did, or 3) the event would have been less severe.
The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all patients enrolled on the trial.

11.1.1 PDMS/CORe will be used as the electronic case report form for this protocol. Adverse events will be documented in the medical record and entered into PDMS/CORe.

11.1.2 These guidelines will be followed for the recording and reporting of adverse and serious adverse events.

a. Baseline events will be recorded in the medical history section of the case report form and will include the terminology event name, grade, and start date of the event.
    i. Baseline events are any medical condition, symptom, or clinically significant lab abnormality present before the informed consent is signed
        a. Hematologic laboratory abnormalities will not be recorded as baseline events for patients with acute leukemia, myelodysplastic

syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase.

b. If exact start date is unknown, month and year or year may be used as the start date of the baseline event.

b. The maximum grade of the adverse event will be captured per course or protocol defined visit date.
c. These adverse events will be recorded in the case report form:
    i. Any grade adverse event that is possibly, probably, or definitely related to the study drug(s).
    ii. All serious adverse events regardless of attribution to the study drug(s).
    iii. Any grade adverse event regardless of attribution to the study drug(s) that results in any dose modification.
d. Hematologic adverse events will not be recorded or reported for studies in patients with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase except for:
    i. Prolonged myelosuppression as defined by the NCI-CTCAE criteria specific for leukemia, e.g. marrow hypocellularity on day 42 or later (6 weeks) from start of therapy without evidence of leukemia (< 5% blasts), or that results in dose modifications, interruptions or meets the protocol definition of DLT or SAE.
e. Serious adverse events will be reported according to institutional policy.
f. Protocol specific language regarding the recording and reporting of adverse and serious adverse events will be followed in the event of discordance between the protocol and Leukemia-specific adverse event recording and reporting guidelines.

11.1.3 Abnormal hematologic values will not be recorded on the case report form. For abnormal chemical values, the apogee or nadir (whichever is appropriate) will be reported per course on the case report form.

11.1.4 All events that are not listed as expected in section 11.1.2 will be collected for the purpose of grading, and determining attribution to study drugs by the PI using the following scale:

Unrelated: The AE is clearly NOT related to the intervention.
Unlikely: The AE is doubtfully related to the intervention.
Possible: The AE may be related to the intervention.
Probable: The AE is likely related to the intervention.
Definite: The AE is clearly related to the intervention.

11.1.5 All grade 3 and greater non-hematological events that are felt to be related to protocol treatment drugs will be documented on the toxicity log and entered into the case report form. The toxicity log and case report form data must reflect relationship to the drug the event is felt to be related to.

11.1.6 Serious Adverse Event Reporting (SAE)
An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32). Pregnancy, drug overdose, and secondary malignancy will be handled as SAE.

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in “The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices”. Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

"Serious Adverse Event Reporting (SAE) for M. D. Anderson-Sponsored IND Protocols":

- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 100 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Investigator Communication with Supporting Companies:

- Any individual expedited SAE reports required by the FDA will be reported to BMS.
- **All Serious Adverse Events must be reported to BMS Worldwide Safety**
  - All SAEs, whether related or unrelated to nivolumab and all pregnancies must be reported to BMS (by the investigator or designee) within 48 hours.
  - All SAEs should be reported via confirmed facsimile (fax) transmission, or scanned and reported via electronic mail to:

    SAE Email Address: Worldwide.Safety@BMS.com

    SAE Fax Number: 609-818-3804

12.0 DISCONTINUATION OF STUDY TREATMENT

A patient's treatment with study drugs may be discontinued for any of the following reasons:

- Clinically significant progressive disease
- Adverse events that are not manageable with dose adjustments and/or optimal medical management, or that, in the opinion of the investigator, pose an unacceptable risk for the patient.
- Investigator decision
- Patient decision (e.g., withdrawal of consent)
- Study termination by Sponsor

Patients who experience toxicity that can be clearly attributed to either nivolumab or to ibrutinib may continue treatment with the other agent. If toxicity cannot be clearly attributed to a single agent, treatment with both agents should be discontinued. Patients who discontinue treatment for reasons other than progressive disease should remain on study and continue to have disease assessments per protocol.

Additional Discontinuation Criteria for Nivolumab

Treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic adverse event, hypersensitivity reactions, and infusion reactions

- Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic adverse event, hypersensitivity reaction, or infusion reaction of <u>any duration</u> requires discontinuation
- Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except those noted below:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
        - AST or ALT > 8 x ULN
        - Total bilirubin > 5 x ULN
        - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN

- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
    - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset.
    - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Any dosing interruption lasting > 6 weeks with the following exceptions:
    - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted
    - Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the Investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing

<u>13.0 CORRELATIVE STUDIES</u>

All correlative studies are optional and failure to collect these studies at any of the specified time-points is not a protocol deviation.

Correlative Studies relating to immunologic response will be collected on a separate IRB-approved Protocol (PA13-0291).

Approximately 30cc of peripheral blood will be collected at the following time-points (pretreatment, C1D1,

C1D15, C2D1, C3D1, end of C3, C5D1, C6D1, end of C6, C8D1, C9D1, end of C9, C11D1, C12D1, end of C12, end of C18, end of C24) and stored in the Leukemia Research Bank. Approximately 6cc of bone marrow aspirate will be collected at the following time-points (pretreatment, C2D1 (only for cohort 1), end of C3, end of C6, end of C9, end of C12, end of C18, end of C24) and stored in the Leukemia Research Bank.

Coevolution of tumor and immune cell heterogeneity following combined ibrutinib and nivolumab therapy in CLL (Catherine Wu, MD, Dana-Farber Cancer Institute, Boston, MA) – We propose a correlative study to analyze both tumor and immune cells in the marrow and peripheral blood microenvironments of CLL, using samples from responders and non-responders, pre- and post-treatment. Using emerging single cell profiling tools to deeply monitor the genetic and molecular processes occurring within tumors from patients undergoing immune modulation, we hope to derive the co-evolutionary trajectories and principles that underlie the success or failure of immunomodulatory therapy. The protocol for freezing whole blood and marrow aspirate is in Appendix 4. The research methods and design are detailed in Appendix 5.

14.0 STATISTICAL CONSIDERATIONS

EFFICACY

A maximum of 72 patients will be enrolled in this Phase II study. Cohort 1 and 3 will enroll up to 24 patients each who were refractory to or relapsed after at least one prior standard therapy or untreated with del(17p) by FISH; Cohort 2 will enroll up to 24 patients who have been on ibrutinib for at least 9 months and have achieved a partial response.

Note: Statistical analysis and sopping rules, and toxicity assessment for Cohort 3 will be same as Cohort 1.

In the first cohort, the primary objective is to evaluate best response during the first 12-month of therapy. The primary efficacy endpoint, best response (BR), is defined as CR or CRi that occurs during the first 12 months of treatment. The optimum two-stage design proposed by Simon will be implemented.[56] We assume a target BR rate of 20% and a BR rate of 5% or lower will be considered not desirable. With a type I error rate of 10% and 80% power, we will enroll 9 patients in the first stage. If no patients achieve BR, the trial will be stopped. If 1 or more out of the first 9 patients have BR, accrual will continue until a total of 24 patients have been enrolled. We will suspend accrual at the end of the first stage, if all 9 patients have been enrolled, yet no responder (CR or CRi) has been observed. At the end of the study, if 3 or more out of the 24 patients achieve BR, the combination treatment will be considered efficacious and is worth further investigation. Under this Simon's two-stage design, the probability of early termination is 63% if the true BR is 5% and the expected sample size is 14.6 patients.

In the second cohort, the primary objective is to evaluate conversion rate during the first 12-month of therapy. The primary efficacy endpoint, conversion rate is defined as the conversion from partial response (PR) to complete response (CR/CRi) that occurs during the first 12 months of treatment. Up to 24 patients will be enrolled in this cohort. The same Simon's optimum two-stage design as described above will be used here in cohort 2. We assume a target conversion rate of 20% and a conversion rate of 5% or lower will be considered not desirable. With a type I error rate of 10% and 80% power, we will enroll 9 patients in the first stage. If no patient converts from PR to CR, the trial will be stopped. If 1 or more out of the first

9 patients achieve conversion, accrual will continue until a total of 24 patients have been enrolled. We will suspend accrual at the end of the first stage, if all 9 patients have been enrolled, yet no conversion has been observed. At the end of the study, if 3 or more out of the 24 patients achieve conversion, the combination treatment will be considered efficacious and is worth further investigation. Under this design, the probability of early termination is 63% if the true conversion rate is 5% and the expected sample size is 14.6 patients.

TOXICITY

The Bayesian approach of Thall, Simon, Estey will be implemented for toxicity monitoring for patients enrolled in cohorts 1 and 2, where toxicity is defined as any grade 3 or higher non-hematological toxicity which is at least possibly related to the treatment.[57] The toxicity, denoted as TOX will be monitored by the Bayesian stopping boundaries calculated based on beta-binomial distributions. We assume as a priori, p(TOX) ~ beta (0.6, 1.4). The study will be stopped for toxicity if Pr(p(TOX)> 0.30 | data) >0.8. That is, we will stop the trial for new patient enrollment if at any time during the study we determine that there is more than 80% chance that the toxicity rate is more than 30%. The toxicity monitoring rule will be applied starting from the 6th patient, and then in cohort size of 6. The toxicity will be considered continuously throughout the study treatment duration. Stopping boundaries corresponding to this toxicity monitoring rule are shown in Table 14.1 below. The operating characteristics for toxicity monitoring are summarized in Table 14.2.

Table 14.1. Toxicity stopping boundaries in cohort size of 6 for patients enrolled in cohorts 1 and 2.

Number of patients	Stop the trial if there are this many patients having toxicity
6	3-6
12	6-12
18	8-18
24	10-24
30	12-30
36	14-36
42	16-42

Table 14.2. Operating characteristics for toxicity monitoring.

True Toxicity Rate	Early Stopping Probability	Average number of patients treated
0.1	0.02	47.3
0.2	0.12	43.4
0.3	0.41	33.8
0.4	0.81	20.7
0.5	0.98	11.7

ANALYSIS PLAN

Summary statistics will be provided for continuous variables. Frequency tables will be used to summarize categorical variables. The best response rate for cohort 1 and conversion rate for cohort 2 will be estimated along with the exact 95% confidence interval.

Data from all patients who receive any study drug will be included in the safety analyses. Patients who entered the study and did not take any of the study drugs and had this confirmed will not be evaluated for safety. The severity of the toxicities will be graded according to the NCI CTCAE v4.0 whenever possible. We will follow standard reporting guidelines for adverse events. Safety data will be summarized by category, severity and frequency. The proportion of patients with AEs will be estimated, along with the Bayesian 95% credible interval. Kaplan-Meier method will be used to assess the overall survival (OS) and progression-free survival (PFS) probabilities. The change of biomarkers over time will be assessed through fitting linear or non-linear mixed effect models.

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and wellbeing of the patient requires immediate intervention, based on the judgment of the investigator or his/her designee. In the event of a significant deviation from the protocol, the investigator will notify the MDACC surveillance committee following the institutional guidelines.

Statistical Language for the correlative studies: Descriptive statistics including plots, mean, median and standard deviations will be used to summarize data. For continuous outcomes, t-test and ANOVA will be used to compare outcome measures across patient characteristics. Dunnett's and Tukey's test that properly adjust for multiplicity in multiple tests will be implemented. Pair-wise comparisons will be performed using pre- and post-therapy samples from each patient. The chi-square (c2) test or Fisher's exact test will be used to test the association between two categorical variables such as disease state and performance status. Both univariate and multivariate logistic regressions will be performed to model prognostic factors.

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APPENDIX 1: SAMPLE OF DRUG ORDERING AND PHARMACY REFERENCE MATERIAL

Nivolumab (BMS-936558) Pharmacy Reference Material

- Nivolumab has a concentration of 10mg/mL and is provided in a 10mL vial. Ten or five vials are provided in a carton.

Initial Orders

- *Following submission and approval of the required regulatory documents, a supply of nivolumab may be ordered from by completing a Drug Request Form provided by BMS for this specific trial. The first request may take place upon screening of the first patient*
- *The initial order should be limited to 20 vials. Allow 5 business days for shipment of drug from BMS receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. All drug product will be shipped by courier in a temperature-controlled container. It is possible that sites may have more than one nivolumab clinical study ongoing at the same time. <u>It is imperative that only drug product designated for this protocol number be used for this study.</u>*
- *<u>Pharmacy supplies not provided by BMS:</u> Empty IV bags/containers, approved diluents, In-line filters and infusion tubing*

Re-Supply

- *Drug re-supply request form should be submitted electronically business days before the expected delivery date. Deliveries will be made Tuesday through Friday.*
- *When assessing need for resupply, institutions should keep in mind the number of vials used per treatment dose, and that shipments may take 14 business days from receipt of request. Drug is not patient-specific. Be sure to check with your pharmacy regarding existing investigational stock to assure optimal use of drug on hand.*

Drug Excursions

- *Drug excursions should be reported immediately to BMS on the form provided with the study-specific drug order form*

Please refer to the most recent version of the Investigator Brochure for additional information.

Storage Conditions & Handling:

- Store at 2-8°C (36-46°F), protect from light, freezing, and shaking.
- If any temperature excursions are encountered during storage, please report these to BMS for assessment via the Temperature Excursion Response Form.
- As with all injectable drugs, care should be taken when handling and preparing nivolumab. Whenever possible, nivolumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents applying aseptic technique.
- Partially used vials should be disposed at the site following procedures for the disposal of anticancer drugs.

After final drug reconciliation, unused nivolumab vials should be disposed at the site following procedures for the disposal of anticancer drugs. For further information, please either discuss with your BMS CSR&O protocol manager or refer to your site IP Destruction policies and procedures

Use Time/Stability: Please refer to section 3.2.3 of the current Investigator Brochure. Due to parameters surrounding the use time of Nivolumab, the time of preparation should be noted in the Pharmacy Source documents [accountability logs] or in study files as required for investigator sponsored research [FDA and GCP]

The administration of BMS-936558-01 injection prepared for dosing nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 20 hours in a refrigerator at under refrigeration conditions (2°-°-8°C (, 36°-46°F) and used within 4for up to 24 hours, and a maximum of 4 hours of the total 24 hours can be at room temperature (20°-25°C, 68°-77°F) and under room light. The maximum 4-hour period under room temperature and room light conditions for undiluted and diluted solutions of BMS-936558-01 injection in the IV bag should be inclusive of the includes the product administration period.

Preparation and Administration:

1. Visually inspect the drug product solution for particulate matter and discoloration prior to administration. Discard if solution is cloudy, if there is pronounced discoloration (solution may have a pale-yellow color), or if there is foreign paticulate matter other than a few translucent-to-white, amorphous particles.

   *Note: Mix by **gently** inverting several times. **Do not** shake.*
2. Aseptically withdraw the required volume of nivolumab solution into a syringe, and dispense into an IV. bag. If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall. **Do not** enter into each vial more than once. **Do not** administer study drug as an IV push or bolus injection
3. Add the appropriate volume of 0.9% Sodium Chloride Injection solution or 5% Dextrose Injection solution. *It is acceptable to add nivolumab solution from the vials into an appropriate pre-filled bag of diluent.*

   Note: Nivolumab infusion concentration must be at or above the minimum allowable concentration of 1 mg/mL.

   Note: It is not recommended that so-called "channel" or tube systems are used to transport prepared infusions of nivolumab.
4. Attach the IV bag containing the nivolumab solution to the infusion set and filter.
5. At the end of the infusion period, flush the line with a sufficient quantity of approved diluents.

Example Dose Calculation [at 3mg/kg]

Total dose should be calculated as follows (assuming total dose volume of 210 mL, 70 kg pt, dose of 3 mg/kg):

- Subject body weight in kg x 3 mg (for the 3 mg/kg cohort) = total dose (mg)
  70 kg x 3 mg/kg = 210 mg
- Total dose (mg) ÷ 10 mg/mL = Amount of solution to be withdrawn from vials
  210 mg ÷ 10 mg/mL = **21 mL**

Example of Total volume of solution to infuse (mL) for a minimum conc solution. – Volume of 10 mg/mL solution (mL) = Volume of Diluent (mL) to add

210 mL – 21 mL = 189 mL

Please note it is perfectly acceptable to dose Nivolumab at a higher drug concentrations, **as long as the total volume of diluted solution is <u>at or above</u> the minimum allowable concentration of 1 mg/mL, below is the calculation based on the above example. Please double check.**

Total dose in mg ÷ Total volume to infuse in mL = Overall drug concentration, mg/mL

210 mg ÷ 210mL = 1 mg/mL

Appendix 2: Inhibitors and Inducers of CYP3A4/5

Inhibitors of CYP3A4/5 are defined as follows. A comprehensive list of inhibitors can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx. The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below. Refer to Section 6.2 on instructions for concomitant use of CYP3A4/5 inhibitors or inducers with ibrutinib.

Inhibitors of CYP3A4/5	Inducers of CYP3A4/5
Strong inhibitors: INDINAVIR NELFINAVIR RITONAVIR CLARITHROMYCIN ITRACONAZOLE KETOCONAZOLE NEFAZODONE SAQUINAVIR SUBOXONE TELITHROMYCIN **Moderate inhibitors:** aprepitant erythromycin diltiazem fluconazole grapefruit juice Seville orange juice verapamil **Weak inhibitors:** cimetidine **All other inhibitors:** amiodarone NOT azithromycin chloramphenicol boceprevir ciprofloxacin delaviridine	Carbamazepine Efavirenz Nevirapine Barbiturates Glucocorticoids Modafinil Oxcarbarzepine Phenobarbital Phenytoin Pioglitazone Rifabutin Rifampin St. John's Wort Troglitazone
fluvoxamine gestodene mibefradil mifepristone norfloxacin norfluoxetine star fruit telaprevir voriconazole	

Source: http://medicine.iupui.edu/clinpharm/ddis/table.aspx

APPENDIX 3: Outside Physician Letter

[**DATE**]

Dear Doctor [_____],
_____ **(name)** is a mutual patient of ours with _____. We have placed him/her on a protocol: "Nivolumab Combined with Ibrutinib for Relapsed, Refractory or High-risk Untreated Patients with Chronic Lymphocytic Leukemia (CLL)" that is being conducted at M.D. Anderson. A copy of the abstract, treatment schedule and consent form will be sent to you for your reference. (**Name)** started treatment on [DATE]. Nivolumab is given on day 1 and 15 of each course (courses 1-24). Each course is 28 days. Ibrutinib is given orally once daily. The principal investigator on this study is Dr. Nitin Jain, and (**name**)'s treating physician is Dr. **[NAME]**.

In order to allow the patient to spend as much time as possible at home, we request your cooperation in the following.

While at home the patient will need the following:

- CBC, platelet count and differential, sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH. These tests will be required at least weekly during the first 3 cycles, and then every 2 weeks, until he/she returns to M.D. Anderson.
- Physical examination is required weekly during the first cycle 1, and then every 2 weeks.
- Please fax all clinic notes, progress notes, labs, imaging and pathology studies to the attention of **[RESEARCH NURSE]** at **[PHONE]** as soon as they become available.
- Please notify [**RESEARCH NURSE**] of hospitalizations for any reason, or any other serious adverse events at telephone number [_____] or pager number [_____].

Please contact Dr. [**NAME**] or myself before adding any new medications as concurrent medications are strictly regulated and must be documented on this protocol.

By signing below, you indicate:
1) Confirmation of your willingness to <u>perform</u> the physical exam, vital signs, ECOG performance status, hematologic and biochemical profiles, and toxicity notation on the dates indicated below;

2) <u>Fax</u> a copy of all patient's visit note as required by the protocol and you deem necessary, (receipt of this documentation will enable us to meet NCI requirements related to the submission of specific paperwork) and allow us to adjust the dose per protocol;

3) <u>Fax</u> a copy of your lab's CLIA certification.

4) All protocol-specific decisions must be made by the MD Anderson investigator/physician.

If you agree with these requests, please sign and return this letter as confirmation that we will receive by

fax a copy of all labs, and a copy of the dictated or handwritten clinic visit notes regarding assessments for the following dates: _____

Signature: _____, Date _____ Tel: _____, Email _____

A follow up visit at MDACC, for evaluation of response and additional testing is scheduled for: _____ [date] _____

For any questions please do not hesitate to contact the research nurse or the Principal Investigator for this study – contact details below.

Sincerely,

Nitin Jain, MD
Principal Investigator
Office: 713-7745-6080; Pager: 713-404-5209; Fax: 713-794-4297
UT MD Anderson Cancer Center
PO Box 301402
Houston, TX 77230-1402

_____

[**RESEARCH NURSE**] RN
Leukemia Research Nurse
Office: [___]; Pager: [___]; Fax: [___]
UT MD Anderson Cancer Center
PO Box 301402
Houston, TX 77230-1402

APPENDIX 4: PROTOCOL FOR FREEZING WHOLE BLOOD

1. Collect blood in a heparin tube (green top) and put tube in ice until freezing.
2. Preparation of freezing buffer: 20% DMSO 80% heat-inactivated FBS (preparation volume accordingly to the number of samples need to be frozen). Keep the freezing buffer cold - it should be cold before adding it to the cell suspension.
3. Blood and freezing buffer should be added in a 1:1 ratio. If different volumes of whole blood are required, adjust the volume of the blood to the volume of the freezing buffer by keeping a 1:1 ratio all the time. Please write on the tube the volume of the blood that you added. Example: Put 750µl of whole blood into a freezing tube (we use Nunc cryotube vials Cat-363401) and ad 750µl of freezing buffer to the blood. Mix well (**do not vortex**) until you get a homogenized solution and then put tube in ice.
4. After preparation of all the freezing tubes containing the cells in freezing buffer, put the tubes in a Mr. Frosty box and put the box in a -80°C freezer. After 48h or more, you can transfer the tubes to liquid nitrogen or you can store them for up to 1 year in -80°C.

Reagents:

DMSO- SIGMA, D8418-100ML

FBS- SIGMA F2442-500ML

Cryotubes- Nunc 363401

Mr Frosty- Thermo Scientific 5100-0001.

APPENDIX 5: COEVOLUTION OF TUMOR AND IMMUNE CELL HETEROGENEITY FOLLOWING COMBINED IBRUTINIB AND NIVOLUMAB THERAPY IN CLL

We propose a correlative study to analyze both tumor and immune cells in the marrow and peripheral blood microenvironments of CLL, using samples from responders and non-responders, pre- and post-treatment. **Using emerging single cell profiling tools** to deeply monitor the genetic and molecular processes occurring within tumors from patients undergoing immune modulation, we hope to derive the co-evolutionary trajectories and principles that underlie the success or failure of immunomodulatory therapy.

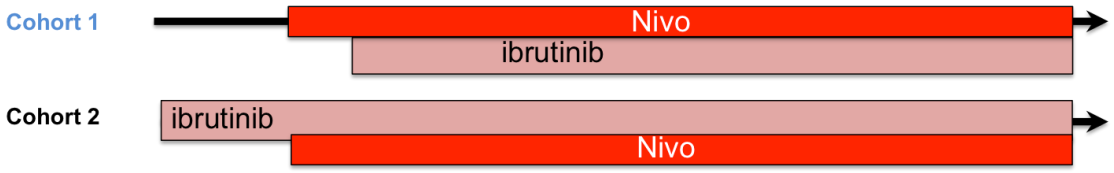
Research Design and Methods:

Aim 1) To define genetic evolution of malignant cells in response to BTK/ITK and PD-1 antagonism. We will study the genetic evolution of cancer somatic alterations through analysis of whole exome sequencing data (WES) pre-/post-therapy (i.e. pre/post ibrutinib, pre/post nivolumab, and pre/post combined ibrutinib/nivolumab) using both germline (saliva) and cancer (either peripheral blood or marrow) from patients at the aforementioned timepoints. Paired RNA-sequencing will be used to validate mutational calls and identify unique transcriptional signatures. From these data, we will estimate tumor purity, then identify somatic point mutations, insertions/deletions, copy number alterations and neoantigens, quantifying their clonal frequencies from pre- and post-treatment samples.

Aim 2) To map distinct molecular states of marrow-infiltrating immune cells at the single cell level, pre- and post-therapy. Using marrow aspirates from the timepoints mentioned in Aim 1, we will utilize a novel, droplet-based high-throughput single cell mRNA sequencing technology to define distinct molecular states of marrow-infiltrating immune cells that associate with therapeutic response or resistance. Thousands of single cells will be encapsulated into droplets with lysis buffer, reverse-transcription mix, and hydrogel microspheres carrying barcoded primers. During reverse-transcription each cDNA is tagged with a unique cellular barcode; droplets are subsequently broken, and all material is linearly amplified before sequencing. Depending on sample availability, multiparameter flow cytometric and multiplexed immunohistochemical analysis of cryopreserved and formalin-fixed paraffin-embedded samples, respectively, will be performed to validate single cell transcriptional signatures and immune populations.

Aim 3) To track tumor specific infiltrating T cell clones by single cell sequencing of paired T cell receptor (TCR) chains. From the peripheral blood, we will sequence paired TCRα and β genes at the single cell level, encoding a fully functioning TCR, in order to identify and monitor T cell clones after therapy that associate with outcome. Over the past year, our group has collaborated extensively with the Broad Technology Labs to develop a high-throughput system for amplifying and sequencing paired TCRα and β genes in single cells, then transfecting the cloned TCR chains into a TCR-deficient T cell line for screening against a library of candidate neoantigens (identified from above) that are used to pulse, and be presented by, patient blood-derived B cells. Monitoring individual T cell clones and the tumor-specific antigens they recognize is critical to understanding coevolution of tumor-T cell responses; recent studies signify the clinical potency of neoantigen-specific TCRs.

Sample Logistics



D1 of Cycle:	1	2	3	4	5	6	7	8	9	10	11	12
PBMCs*	x	x	x			x			x			x
BM aspirate+	x	x	x			x			x			x
Saliva	x											
Unstained slides from FFPE BM Bx tissue block	x	x	x			x			x			x

X = end of Cycle 1 BM aspiration
X = end of cycle (3,6,9,12) BM asp/bx

Sample volume

*2-3 purple top tubes (~10 cc's each)
+1-2 purple top tubes

Sample preparation (in order of preference):

1st: Freeze whole blood/aspirate per protocol

OR

2nd: Immediate RBC lysis (within 3 hours) followed by cryopreservation.

OR

3rd: Immediate Ficoll (within 3 hours), followed by cryopreservation.

****Mail o/n in batches.**